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ORIGINAL ARTICLE

Acetazolamide: A New Treatment for Visual Vertigo

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ABSTRACT

Visual vertigo is a disorder characterised by symptoms of dizziness, vertigo, unsteadiness, disorientation, and general discomfort induced by visual triggers. It is currently treated with vestibular rehabilitation therapy, with no effective pharmacotherapy available for treatment-resistant cases. The objective of this study was to evaluate the efficacy of oral acetazolamide in improving symptoms of visual vertigo. A comparative case series of adult patients clinically diagnosed with visual vertigo was conducted from January 1992 to May 2015. Patients without a full neurologic or otorhinolaryngologic work-up, negative magnetic resonance imaging (MRI), and an organic cause for their symptoms were excluded. The identified patients were then contacted by phone to complete a voluntary symptom survey. Main outcome was the subjective reported percentage in symptom improvement. Secondary outcomes were subjective improvement by symptom triggers. The participants were retrospectively divided into three groups based on their treatment with acetazolamide: currently on acetazolamide, terminated acetazolamide, or never initiated acetazolamide. Fifty-seven patients met the inclusion criteria and were willing to complete the phone survey (19 currently on acetazolamide, 27 terminated acetazolamide, and 11 never initiated therapy). Overall symptomatic improvement was reported by 18 (94.7%) patients currently on acetazolamide, 18 (66.7 %) who terminated acetazolamide, and 5 (45.5%) who never initiated therapy, varying significantly by group ($p = 0.0061$). Greatest improvement was reported in symptoms triggered by being a passenger in a car. These results show that acetazolamide has a positive association with improvement of symptoms of visual vertigo.

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Introduction

Visual vertigo (VV) is a disorder characterised by symptoms of dizziness, vertigo, unsteadiness, disorientation, and general discomfort induced by visual triggers.[1,2] Patients typically present with discomfort instigated by walking through shopping centres, being a passenger in a car, watching trains moving at a railroad crossing, watching action programs on television or movies, certain designs and patterns, as well as fluorescent lights. However, VV is different from "true" rotational vertigo, because the patients do not experience "rotation" of their environment but rather the actual movement in their environment triggers their symptoms.[2] Symptoms typically occur in the latent phase after an acute vestibular insult, such as vestibular neuritis, benign paroxysmal positional vertigo, or a migraine event.[1–3] Acute vertigo usually subsides after several weeks, but occasionally the patient will notice lingering visual discomfort and symptom exacerbation from moving objects.[1] The patient is often frustrated and anxious about their symptoms and lack of symptom resolution, but the level of anxiety was found to be similar among all types of vestibular disorders, thus pointing against VV being a disease of pure psychogenic origin.[2]

VV is currently thought to be a disease of visual dependence. Three sensory systems are involved in human spatial orientation—cerebellar (proprioception), vestibular, and visual systems. In order to maintain balance, two out of the three systems are required to function, thus the basis of the Romberg test.[1] In situations where the sensory systems are in conflict, the brain must correct the sensory input in order to maintain proper spatial orientation. In visually dependent individuals, the brain relies on the visual system to maintain spatial orientation in times of sensory conflict.[3,4] These individuals were found to become

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destabilised and disoriented by tilted or moving surroundings in a study by Witkin and Asch in 1948.[5] It has been hypothesised that an acute vestibular insult could enhance visual dependence, thus creating visual vertigo, particularly in patients who were visually dependent prior to insult.[3]

Visual vertigo is currently a clinical diagnosis based on the patient's history of disease presentation. Several questionnaires have been designed over the years to screen for symptoms and help evaluate treatment efficacy, such as the Situational Characteristic Questionnaire (SCQ).[3] More recently, Dannenbaum et al. created a questionnaire specifically for VV using the SCQ.[6] The questionnaire uses an analog scale to grade the intensity of dizziness triggered by daily situations typically inducing visual vertigo, including being a passenger in a car, walking in a supermarket, being under fluorescent lights, being at an intersection, going up escalators, being at shopping centres, watching movies, patterns, and watching television.[6]

Traditional treatments for this disorder involve vestibular rehabilitation (e.g., Cawthorne-Cooksey approach, walking exercises), virtual reality simulators of moving objects, as well as graded exposure to optokinetic stimulation.[1,7] The goal of therapy is to promote desensitisation to visual stimuli and increase tolerance.[1] Train observation exposure therapy was recently described, which was thought to function by using stationary objects in the field of view to help stabilise the image of moving objects.[8]

In 1991, Farris and Hester described a series of seven patients with visual vertigo, of whom six experienced some or complete relief after being treated with oral acetazolamide.[9] The idea behind acetazolamide arose from reports of improvement of dizziness symptoms in familial episodic vertigo treated with the medication.[10] Based on the 1991 case series, the VV patients seen at the Dean McGee Eye Institute have been treated with acetazolamide since 1986. This retrospective study evaluated the efficacy of acetazolamide as treatment for visual vertigo.

Methods

A retrospective chart review was carried out on patients who had been diagnosed with visual vertigo at our institute from January 1992 to May 2015. Patients were identified using the International Classification of Diseases Ninth Revision (ICD 9) code 780.4: "dizziness and giddiness," which was used by study investigator (B. K.F.) to code for visual vertigo during the study period. All the charts were then reviewed to confirm the diagnosis of visual vertigo, and patients not carrying the diagnosis were excluded. Patients who were not diagnosed with visual vertigo by B.K.F. or had concurrent organic cause of their vertigo symptoms after the initial encounter (e.g., brain lesion, head trauma, migraine-induced vertigo, or bilateral symmetric peripheral vestibular loss) were excluded as well. Deceased patients were excluded from the study. Patients were included in the study if they had a history of a vestibular insult (such as viral vestibulitis) that was deemed resolved or inactive by the referring neurologist or otorhinolaryngologist. Visual vertigo was diagnosed clinically based on a symptom trigger and absence of organic disease.[6] All patients had undergone magnetic resonance imaging (MRI), a full examination by an otorhinolaryngologist, and a full ophthalmic examination. Demographic data, including age, age at onset, age at diagnosis, ethnicity, sex, general medical history, vestibular medical history, ocular medical history, treatment plan, and dose of acetazolamide prescribed, were collected. Per our protocol, the vast majority of our patients were started at 250 mg of oral acetazolamide daily and were slowly titrated up based on symptomatic feedback, unless the patient had a very low medication tolerance or insisted starting low, at which point they were started on 125 mg daily dose.

The identified patients were then contacted to complete a voluntary symptomatic phone survey using the modified Dannenbaum questionnaire.[6] Two phone calls were attempted for each patient for every available phone number in our medical record system. After a verbal informed consent was obtained over the phone, the patients were questioned about symptom improvement, current status of acetazolamide therapy, current dosage, or their reason for therapy cessation. The study was Health Insurance Portability and Accountability Act (HIPAA) compliant, and institutional review

board (IRB) approval was obtained. This study adhered to the tenets of the Declaration of Helsinki.

The participants were then divided into three groups: currently on acetazolamide, terminated acetazolamide, or never initiated acetazolamide. The groups' demographics were compared using the Kruskal-Wallis test (for continuous variables) and chi-square tests for independence or Fisher's exact test (for categorical variables). Only the self-reported improvement in symptoms as a percent score was tested in a series of Wilcoxon rank-sum tests under the two-group classification (currently or previously on acetazolamide vs. never initiated acetazolamide). Bonferroni's method was used for multiple comparisons. A two-sided p value of <0.05 defines statistical significance.

Results

A total of 705 patients were identified to have been diagnosed with visual vertigo from January 1992 to May 2015. After a thorough chart review, 323 patients were diagnosed with visual vertigo. Phone attempts were made for all of these patients, and we were able to reach 85 patients. Of these, 64 patients agreed to participate in the phone survey. Five patients were excluded for not being treated by B.K.F. and 2 patients were excluded after reporting an organic cause for their symptoms (inner ear tumour and contraceptive-induced vertigo) for a total of 57 patients undergoing analysis (19 currently on acetazolamide, 27 terminated acetazolamide, and 11 never initiated therapy). None of the patients were started on a new medication within 1 month prior to starting acetazolamide.

The majority of the sample population was Caucasian (98.2%) and female (80.7%), with an average age of onset of 47.2 ± 15.6 years (Table 1). History of migraine was reported in 29.8% of the total patients, and a previous history of a vestibular disorder (decreased hearing, benign paroxysmal positional vertigo [BPPV], labyrinthitis, Meniere's disease) was reported in 56.1%, with no statistically significant difference among the three subsets (p = 1.0000 for migraine and p = 0.0895 for vestibular disorders). The characteristics of the non-participants (Table 2) were similar to the study participants, except for a slightly higher prevalence of vestibular disorders among the study participants.

Overall symptomatic improvement was reported by 18 (94.7%) patients currently on acetazolamide, 18 (66.7 %) who terminated acetazolamide, and 5 (45.5%) who never initiated therapy, varying significantly by group (p = 0.0061). Patients who had ever received acetazolamide reported significantly greater improvement in overall dizziness (p = 0.0020) than those in the "never took" group.

To identify whether any specific symptoms were improved over others, the patients currently or previously on acetazolamide ("ever took" group) were compared against the "never took" group; dizziness triggered by being a passenger in a car (p = 0.0017), watching cars at an intersection (p = 0.0062), watching action movies (p = 0.0066), watching television (p = 0.0072), and being in a crowd (p = 0.0214) showed significant improvement compared with other symptoms by Wilcoxon rank-sum test (Table 3). However, after adjustment for multiple comparisons using the Bonferroni correction, only the "being a passenger in a car" was significantly different between the two groups, $p < 0.0154$.

The daily dose was significantly higher in the patients currently on acetazolamide (447 ± 248 mg/day) compared with the patients who terminated acetazolamide (284 ± 172 mg/day), p = 0.0013. Of the patients in the "terminated acetazolamide" group, the therapy continued for an average of 9 months (median: 3 month, range: 1–48 months). Of the patients in the "currently on acetazolamide" group, the average duration of therapy was 58 months (median: 48 months, range: 1–240 months).

The most common reason for not initiating therapy was choosing another medication for symptom control (Table 4). Alternative medications included oral meclizine or diazepam. The most common reason for terminating therapy was medication side effects (59.3%), followed by lack of symptom improvement (22.2%) (Table 5). Fatigue was the most common

Table 1. Study participant demographics.

		Ever taken acetazolamide group				
Demographic	Total participants	Total	Currently taking	Terminated therapy	Never initiated therapy group	*p* value
Participants	57	46	19	27	11	< 0.0001
Age at diagnosis	51.6 ± 15.9	48.8 ± 15.7	50.8 ± 13.8	47.4 ± 17.1	63.1 ± 11.2	0.0071
Age at onset	47.2 ± 15.6	45.4 ± 16.0	47.3 ± 13.3	44.1 ± 17.8	54.7 ± 12.0	0.0662
Symptom duration (years)	4.4 ± 6.4	3.4 ± 3.4	3.6 ± 3.0	3.3 ± 3.7	8.4 ± 12.4	0.7387
% Female	46 (80.7%)	39 (84.8%)	17 (89.5%)	22 (81.5%)	7 (63.6%)	0.1952
% Caucasian	54 (94.7%)	43 (93.5%)	19 (100%)	24 (88.9%)	11 (100%)	1.0000
Migraine history	17 (29.8%)	13 (28.2%)	6 (31.6%)	7 (25.9%)	4 (36.4%)	1.0000
Vestibular history	32 (56.1%)	28 (60.8%)	14 (73.7%)	14 (51.8%)	4 (36.4%)	0.1839

Note. All average values are reported as mean ± standard deviation. The "ever taken acetazolamide" group is presented as a total as well as split between the patients currently taking acetazolamide and those who have terminated therapy. Patients with "unknown" ethnicity were counted as "non-Caucasians." Vestibular history was defined as having a previous vestibular disorder (e.g., decreased hearing, BPPV, labyrinthitis, Meniere's disease). *p* value represents the comparison between the "ever taken acetazolamide" and the "never initiated therapy" groups.

Table 2. Study non-participant demographics.

		Unable to be reached group				
Demographic	Total non-participants	Total unable to reach	Answering machine	Phone disconnected	Refused to participate group	*p* value
Non-participants	266	245 (92.1%)	157 (64.1%)	88 (35.9 %)	21 (7.9%)	<0.0001
Age at diagnosis	47.3 ± 13.6	46.9 ± 13.6	46.6 ± 12.4	47.5 ± 15.5	51.5 ± 13.9	<0.0001
Age at onset	43.1 ± 14.5	43.0 ± 14.7	42.6 ± 14.1	43.6 ± 15.7	44.7 ± 12.6	<0.0001
Symptom duration (years)	4.1 ± 6.4	3.9 ± 6.3	4.0 ± 6.3	3.9 ± 6.4	6.8 ± 7.0	0.6860
% Female	186 (69.9%)	170 (69.4%)	115 (73.2%)	55 (62.5%)	16 (76.2%)	0.6859
% Caucasian	166 (62.4%)	155 (63.3%)	98 (62.4%)	57 (64.8%)	11 (52.4%)	0.4511
Migraine history	94 (35.3%)	88 (35.9%)	63 (40.1%)	25 (28.4%)	6 (28.6%)	0.6613
Vestibular history	90 (33.8%)	84 (34.3%)	55 (35.0 %)	29 (32.3%)	6 (28.6%)	0.7711

Note. Study non-participants were defined as patients who were diagnosed with visual vertigo but were not able to be reached for a telephone survey or who refused to participate in the study. Patients with "unknown" ethnicity were counted as "non-Caucasians." Vestibular history was defined as having a previous vestibular disorder (e.g., decreased hearing, BPPV, labyrinthitis, Meniere's disease). *p* value represents the comparison between the "unable to reach" and the "refused to participate" groups.

Table 3. Symptom improvement by environmental stimuli.

Environmental stimulus	Never initiated therapy (median score)	Currently or previously on acetazolamide (median score)	*p* value	Adjusted *p* value
Riding as passenger in car	0.0	50.0	**0.0017**	**0.0154**
Road Intersection	0.0	50.0	**0.0062**	0.0554
Action movies	0.0	35.0	**0.0066**	0.0595
Television	0.0	50.0	**0.0072**	0.0644
Crowd	0.0	30.0	**0.0214**	0.1927
Patterns	0.0	45.0	0.0137	0.1237
Grocery store	2.0	50.0	0.0990	0.8912
Escalator	0.5	25.0	0.1887	1.0000
Fluorescent lights	0.0	22.5	0.6787	1.0000

Note. Scores represent deviation from median of symptom improvement subjectively reported by study participants as a percentage. Wilcoxon rank-sum comparison of subjective percent symptom improvement then compares the "currently on acetazolamide +"terminated acetazolamide" vs. "never initiated therapy" groups to determine the strength of the correlation as a *p* value. Adjusted *p* values were calculated by the Bonferroni method to correct for multiple comparison parameters.

reported symptom, followed by numbness and tingling of the extremities.

Discussion

Acetazolamide has a positive association with improvement of symptoms of visual vertigo, with a trend for greater improvement in more dynamic movements in the environment (car passenger, intersections, action movies, television, and crowds). Considering the dose difference between the three groups, acetazolamide was more effective when taken in doses of 500 mg a day. Since our starting dose is usually 250 mg daily, this suggests

Table 4. Reasons for not initiating therapy.

Reason	No. of participants	Percent
Took another medication	5	45.5%
Feared interactions	2	18.2%
Did not want more medications	1	9.1%
Pregnancy	1	9.1%
Other	2	18.2%

Table 5. Reasons for terminating acetazolamide.

Reason	No. of participants	Percent
Side effects	16	59.3%
Lethargy or fatigue	5	18.5%
Tingling or numbness	4	14.8%
Stomach, nausea, or upset stomach	3	11.1%
Headache	2	7.4%
Odd taste	2	7.4%
Diuretic effect	2	7.4%
Hallucinations	1	3.7%
Kidney stones	1	3.7%
Hypotension	1	3.7%
Other	8	29.6%
Could not recall	4	14.8%
Switched medications	2	7.4%
Symptoms improved	1	3.7%
Taking too many medications	1	3.7%
Lack of symptom improvement	6	22.2%

Note. While 27 patients terminated acetazolamide, several patients reported multiple reasons for stopping therapy.

that these patients respond to the initial therapy and wish to increase the dose for greater benefit. Some patients prefer to start slower, at a lower dose and slowly increase over time. These would start at 125 mg/day, with a maximum dose targeted at 1000 mg/day if needed, and tolerated, based on regular patient feedback. Interestingly, patients who took acetazolamide for a short time still reported significant improvement compared with those naïve to therapy (p = 0.0307), which could suggest placebo effect or spontaneous improvement in symptoms. However, the group who never initiated therapy reported minimal to no improvement in symptoms. The side-effect profile of acetazolamide was significant (16/57, 28%), but no serious drug reaction to the medication occurred in our patient sample.

The exact mechanism of action of acetazolamide in the treatment of visual vertigo symptoms is unknown. The nerve impulses in the cochlea and the vestibular system are dependent on a Na^+ and a K^+ gradient for proper function, which is regulated by Na,K-ATPase and carbonic anhydrase.[11] Acetazolamide is a potent carbonic anhydrase inhibitor that decreases the direct current potential of the endolymphatic sac of the cochlea, thus lowering hydrostatic pressure in the vestibular system.[12,13] Therefore, it is possible that the lowered hydrostatic pressure suppresses the vestibular response, thus reducing the vertigo sensation.

Another possibility involves a mechanism more closely related to its original use in the treatment of episodic cerebellar ataxia type 2, also known as acetazolamide-responsive cerebellar ataxia, where affected individuals report episodic symptoms of vertigo, visual disturbances, and ataxia that respond to oral acetazolamide treatment.[14] The cerebellum processes vestibular, proprioceptive, and visual stimuli to control balance. Atrophy of the cerebellar vermis has been reported in episodic cerebellar ataxia on MRI.[15] The atrophied cerebellum may be unable to process the plethora of moving visual stimuli, thus creating a sensation of vertigo and overall discomfort. Acetazolamide has been shown to improve visual stimuli recognition and processing when compared with controls.[16] Therefore, it is possible that acetazolamide may act directly on the cerebellar visual processing centre and enhancing its filtering function. Cerebellar atrophy was not identified in those patients who did undergo neuroimaging in our study.

Specific limitations of our study are its retrospective nature, the subjective symptom-based diagnosis of the disease as well as improvement, and the relatively low patient participation. Unfortunately, the low prevalence of this condition makes randomised clinical trials challenging but may be possible in the future as a multi-centre study. Due to the subjective nature to the disease with no objective tests available for diagnosis, clinical assessment as well as MRI and evaluations by otorhinolaryngology and neurology remain the only options. Although the end point in our study was a subjective marker in self-reported symptom improvement, which carries a fair amount of bias due to the placebo effect, we were fortunate to have three different groups in our study, which reached statistical significance. The adverse side effects of acetazolamide, particularly paresthesias and dysgeusia, may encourage only the patients actually receiving benefit to continue

taking the medication. Considering the debilitating nature of the disease and the low serious side-effect profile, oral acetazolamide appears to be a useful tool in management of visual vertigo.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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